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**Erk Negative Feedback Control Enables Pre-B Cell Transformation and Represents a Therapeutic Target in Acute Lymphoblastic Leukemia.**

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**Public Summary:**

Studying mechanisms of malignant transformation of human pre-B cells, we found that acute activation of oncogenes induced immediate cell death in the vast majority of cells. Few surviving pre-B cell clones had acquired permissiveness to oncogenic signaling by strong activation of negative feedback regulation of Erk signaling. Studying negative feedback regulation of Erk in genetic experiments at three different levels, we found that Spry2, Dusp6, and Etv5 were essential for oncogenic transformation in mouse models for pre-B acute lymphoblastic leukemia (ALL). Interestingly, a small molecule inhibitor of DUSP6 selectively induced cell death in patient-derived pre-B ALL cells and overcame conventional mechanisms of drug-resistance.

**Scientific Abstract:**

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